

REMARKS

Claims 1 and 18 have been amended to obviate the rejection for lack of antecedent basis, and to clarify the claims. Applicants understand, with respect to claim 1, that the preamble has been disregarded in favor of consideration only of the active steps; the preamble has been modified to more closely reflect the active steps involved. Claim 1 has further been clarified to indicate that the nanoparticles bound to the target remain liquid at all temperatures measured. This is clear from the specification; for example, see page 8, lines 7-10 and lines 13-16. Thus, no new matter has been added and entry of the amendment is respectfully requested.

The Rejections Under 35 U.S.C. § 102(e)

All claims, except claims 3, 21, 73 and 75, were rejected as assertedly inherently anticipated by Ostensen (U.S. 6,375,931). Applicants believe this rejection is in error for the very reasons set forth by the Office in proposing the rejection. As noted by the Office on page 5, quoting Ostensen, Ostensen is dealing with a gas dispersion containing microbubbles. It is the expansion of the microbubbles that accounts for the contrast enhancement observed by Ostensen during the radiation with ultrasound. It is explicit in the present claims that all measurements are taken where the nanoparticles are in liquid form. Therefore, Ostensen clearly does not anticipate the invention, as Ostensen relies on expansion of gas bubbles to enhance contrast whereas applicants' claims require liquid nanoparticles.

It is not clear why the Office asserts, also on page 5, that perfluorobutane is a liquid at room temperature when the Ostensen patent itself states that at 9°C (well below room temperature) the perfluorobutane is in the form of microbubbles. Ostensen is observing an entirely different

phenomenon from that set forth in the claims herein which require that liquid nanoparticles are measured at two different temperatures, not particles containing microbubbles as described by Ostensen.

Ostensen is quite specific that they are using “gas-containing contrast agent preparations which promote controllable and temporary growth of the gas phase *in vivo* following administration” (see Abstract, for example). No liquid preparations are ever described or, apparently, intended.

The Rejection Under 35 U.S.C. § 103

All claims, including those not within the scope of the rejection for anticipation, were rejected on the basis of obviousness over Ostensen. Ostensen not only does not anticipate; Ostensen does not suggest the invention as claimed. Ostensen describes using “a diffusible component capable of diffusion *in vivo* into the dispersed gas so as at least transiently to increase the size thereof” as set forth in column 2, lines 53-54. The increase in bubble size due to temperature alone described in column 35 seems to be discussed independently of the focus of the Ostensen disclosure.

In any event, it is evident that there is no suggestion in Ostensen that an enhancement of temperature of a liquid nanoparticle would improve its reflectivity and thus its ability to serve as a contrast agent as required by the claims. The stated reason for improvement in gas-based formulations – increased volume – would not apply to liquids. Thus, applicants respectfully request that this basis for rejection be withdrawn.

Applicants also note that the claims requiring perfluorooctane were not considered anticipated because although Ostensen mentions this compound, it is not used in the examples. This

is because the contrast agent itself is never composed of this compound. Ostensen, rather, employs this compound, among others, as a diffusion agent which serves to enlarge the microbubbles that are already there.

At column 3, Ostensen describes the nature of the gas dispersions as including substances that are substantially or completely in gaseous form at the normal human body temperature of 37°C among these compounds are listed halogenated low molecular weight hydrocarbons containing up to seven carbon atoms (column 3, lines 27-28). The entire discussion in column 3 relates to the gas-containing contrast agent formulations.

As stated above, Ostensen's procedure involves use not only of a gaseous dispersion formulation, but also a "diffusible component capable of diffusion *in vivo* into the dispersed gas so as at least transiently to increase the size thereof." It is only in this category that perfluorooctanes are even mentioned. This, perfluorooctanes are not the part of the contrast formulation that contains microbubbles, but rather in an *additional* composition designed to diffuse into the primary contrast agent. It is simply not the case that Ostensen suggests the use of perfluorooctane as the basis for the contrast agent of which reflectivity is measured.

In summary, the invention resides in the finding that increasing the temperature of liquid nanoparticles which are bound to a target can enhance the reflectivity of the target, not only indicating that the image can be enhanced by increasing the temperature, but also, as described in the specification, permitting the enhanced image to serve as a temperature gauge. Ostensen, on the other hand, relies on expansion of gaseous microbubbles to provide a transient enhancement of contrast – an entirely different approach based on a different principle. For these reasons, applicants believe that the rejections over Ostensen may properly be withdrawn.

Unger

Applicants note with appreciation that the rejection over Unger is moot, but wish to comment on the remarks made by the Office concerning the Declaration of Gregory Lanza. The Office states that “the declaration is not commensurate with the scope of the claims as it appears to refer(s) only to the system described in the above referenced application and not to the individual claims of the application.” Applicants do not know which application is the “above referenced” one, but note that the declaration has very little to do with the claimed invention, but rather constitutes an interpretation of the cited Unger document. Since the contents of the declaration are directed to interpretation of the cited document and not to the claimed invention, there is no issue of scope.

Again, applicants appreciate that the rejection over Unger has evidently been overcome.

CONCLUSION

The claims have been amended to correct informalities and for clarity. The claims as proposed make clear that the nanoparticles subjected to ultrasound imaging or reflectivity measurements are liquid nanoparticles and are not gaseous. The only document cited against these claims, Ostensen, clearly relies on the gaseous nature of the contrast medium used in that document for any effect on reflectivity. Accordingly, respectfully, applicants believe that Ostensen is irrelevant to the invention as claimed and request that claims 1, 3, 7-8, 13, 17-18, 21, 25-26, 31, 35 and 68-77 be passed to issue forthwith.

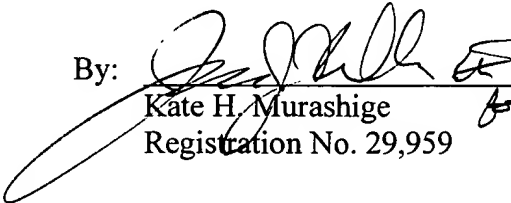
If a telephone discussion would be helpful in expediting the prosecution of this application, the Examiner is encouraged to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532512000500.

Respectfully submitted,

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